

# Re-defining response and treatment effects for neuro-oncology immunotherapy clinical trials

David A. Reardon · Hideho Okada

Received: 3 December 2014 / Accepted: 16 February 2015 / Published online: 24 February 2015  
© Springer Science+Business Media New York 2015

**Abstract** In much of medical oncology, including neuro-oncology, there is great interest to evaluate the therapeutic potential of immune-based therapies including vaccines, adoptive T cell strategies and modulators of immune checkpoint regulators such as cytotoxic T lymphocyte antigen 4 and programmed death 1. Immune-based treatments exert an indirect anti-tumor effect by generating potent, tumor-targeting immune responses. Robust anti-tumor immune responses have been shown to achieve encouraging radiographic responses across the spectrum of applied immunotherapeutics which are felt to be indicative of a bona fide anti-tumor effect. Conversely, worsening of imaging findings, particularly early in the course of immunotherapy administration, can be challenging to interpret with growing evidence demonstrating that at least a subset of such patients ultimately will derive meaningful clinical benefit. The immune related response criteria were generated to provide guidance regarding the interpretation of such complex imaging findings, for general medical oncologists prescribing immunotherapeutics. An analogous effort that addresses challenges associated with imaging assessment and incorporates nuances associated with neuro-oncology patients is underway and is referred to as the immunotherapy response assessment in neuro-oncology criteria.

**Keywords** Immunotherapy · Glioblastoma · Vaccine · Immune checkpoint inhibitor · Pseudoprogression

## Clinical development of immunotherapeutics for neuro-oncology

The application of therapeutic strategies to harness the immune system against cancers, initially conceived by Coley in 1891 with the administration of streptococcal organisms to inoperable cancer patients [1], has emerged to become a leading area of oncology intervention. Current enthusiasm for broadening immunotherapy approaches for cancer indications including neuro-oncology derives from exciting results generated by three different classes of immune-based therapies against challenging cancer indications including vaccines, adoptive T cell therapies and immune checkpoint modulating agents.

In 2010 the US Food and Drug Administration approved sipuleucel-T, the first, non-viral vaccine for cancer therapy. Sipuleucel-T is a cancer vaccine consisting of autologous peripheral blood mononuclear cells activated ex vivo with a recombinant fusion protein consisting of prostate antigen prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor. Although strategies to generate effective therapeutic cancer vaccines over the past decades have been disappointing [2], a 4 month survival benefit was observed among metastatic, castration-resistant prostate cancer patients treated in a double-blind, placebo-controlled multicenter phase III trial with sipuleucel-T [3]. Of note, although sipuleucel-T treated patients had a 22 % hazard ratio reduction for overall survival and an improvement in 3-year survival from 23 to 32 %, progression-free survival did not differ compared to placebo controls.

---

D. A. Reardon (✉)  
Center for Neuro-Oncology, Dana-Farber Cancer Institute, 450  
Brookline Avenue, Dana-2134, Boston, MA 02215, USA  
e-mail: david\_reardon@dfci.harvard.edu

H. Okada  
Department of Neurological Surgery, University of California,  
San Francisco, 505 Parnassus Avenue, M-7790, San Francisco,  
CA 94143-0520, USA

A wide array of vaccine therapeutics are in clinical development for neuro-oncology [4], including several that are in advanced evaluation for glioblastoma. Encouraging preliminary efficacy was recently reported in the first completed, placebo controlled clinical trial evaluating a vaccine for glioblastoma patients [5]. In this study, 124 newly diagnosed glioblastoma patients were randomized to receive ICT107, a vaccine consisting of autologous dendritic cells pulsed against six tumor-associated glioma antigens, or placebo, along with standard temozolomide chemoradiotherapy. Although outcome data from this study are still maturing, progression-free survival was significantly prolonged along with a non-significant trend of improved survival for vaccine recipients. Rindopepimut, a peptide targeting EGFRvIII conjugated to the immunoadjuvant keyhole limpet hemocyanin (KLH), is also in advanced development for glioblastoma patients with tumors expressing EGFRvIII [6]. A placebo-controlled, randomized phase III trial has recently completed accrual for newly diagnosed patients (NCT01480479) while a randomized phase II study among recurrent patients recently reported a 3.2 month survival benefit and a 57 % reduction in the overall survival hazard ratio for rindopepimut recipients compared to placebo controls [7]. A double-blind, placebo-controlled, randomized phase III study of DCVax-L, a vaccine consisting of autologous dendritic cells pulsed with tumor lysate, is also underway for newly diagnosed glioblastoma patients (NCT00045968). HSPPC-96, a vaccine generated from individual tumor-specific heat shock protein peptide complexes [8], is being evaluated in a randomized phase II study for recurrent glioblastoma patients (NCT01814813). Finally, SL-701, a peptide vaccine targeting glioma stem cell antigens conjugated with GM-CSF and administered with topical imiquimod, is also being evaluated in a large, single-arm phase II study (NCT02078648). Beyond glioblastoma, a clinical trial evaluating a tumor-based vaccine is underway for patients with recurrent medulloblastoma or primitive neuroectodermal tumors (NCT01326104). In addition for low-grade glioma patients, a tumor lysate/autologous dendritic cell vaccine is currently being evaluated (NCT01635283) and a vaccine against mutant isocitrate dehydrogenase 1 has recently initiated accrual (NCT02193347).

Adoptive T cell therapies, particularly the use of chimeric antigen receptor (CAR) T cells, have generated unprecedented durable remissions in patients with refractory leukemia [9–13]. Strategies to engineer autologous T cells to express chimeric antibodies against tumor antigens have been in development for over 20 years, but have been limited by inadequate expansion and persistence of engineered T cells. These limitations have been overcome by more recent CARs which incorporate additional co-

stimulatory signals to prevent activation-induced cell death, and to sustain proliferation and potentiation of T cell effector functions [14]. A highly exciting initial report documented durable remission in 2 patients with refractory pre-B cell acute lymphoblastic leukemia (ALL) following treatment with CTL019, an autologous T cell product engineered to express an anti-CD19 single chain Fv domain fused to the CD3-zeta domain and the co-stimulatory molecule CD137 (4-1BB) [10]. In a follow-up study, 27 of 30 (90 %) of patients with refractory pre-B ALL achieved a complete remission which was sustained for up to 6 months in 73 % following CTL019 therapy [9]. Clinical trials evaluating CAR T cells are in early development for solid tumor patients including clinical trials for glioblastoma patients targeting HER2 (NCT01109095), IL13R $\alpha$ 2 (NCT02208362) and EGFRvIII (NCT01454596).

Monoclonal antibodies targeting immune checkpoint mediators have achieved unprecedented anti-tumor activity including apparent cures against metastatic melanoma, a malignancy with historical outcome as poor as glioblastoma, as well as other challenging solid tumors. Two key inhibitory immune checkpoints that have been successfully targeted to date for cancer therapy include cytotoxic T-lymphocyte antigen 4 (CTLA-4), which functions normally to control early T cell activation, and programmed death 1 (PD-1), a key component of the normal immune system that regulates T cell activation, peripheral tolerance and bystander tissue damage during immune responses [15, 16]. Ipilimumab, a humanized IgG1 anti-CTLA-4 MAb, was approved for advanced, unresectable melanoma based on improved survival in two separate, randomized phase III studies. In the first study, ipilimumab therapy led to a 4 month improvement in overall survival (HR 0.66;  $p = 0.0026$ ) and an 11 % radiographic response rate compared to only 1.5 % of control patients [17]. In the second study, ipilimumab plus dacarbazine had higher median overall survival as well as improved survival at 1, 2 and 3 years compared to dacarbazine plus placebo [18]. Of note in both of these studies, median PFS did not differ between treatment arms although the PFS hazard ratio was reduced for ipilimumab receiving patients. Furthermore, long-term follow-up of 177 advanced melanoma patients treated with ipilimumab revealed a median duration of tumor response of 7.3 years and an unprecedented 5 year survival rate of approximately 20 % [19].

Dramatic results have also been observed with therapeutics against PD-1 and its ligand, PD-L1. Accelerated approval was recently granted to pembrolizumab, a humanized PD-1 blocking MAb, by the FDA for advanced melanoma based on a 24 % overall response rate (ORR) [20]. Sustained radiographic responses have also been observed with nivolumab, a humanized anti-PD-1 MAb for advanced solid tumors [21], as well as lambrolizumab, an

anti-PD-L1 MAb for advanced melanoma [22]. Furthermore, dramatic rates of sustained radiographic responses have been observed following combination of CTLA-4 and PD-1 blockade, consistent with complementary mechanisms of anti-tumor activity [23]. Further clinical development of therapeutics targeting CTLA-4, PD-1 and PD-L1, as well as other key immune checkpoint mediators, is rapidly expanding in oncology, including neuro-oncology. Clinical trials for glioblastoma patients evaluating nivolumab (NCT02017717), nivolumab plus ipilimumab (NCT02017717), pembrolizumab (NCT02054806) as well as lambrolizumab (NCT01693562) are underway with additional approved studies pending activation. In addition, clinical trials are also currently active evaluating ipilimumab for patients with melanoma brain metastases (NCT02115139 and NCT02107755).

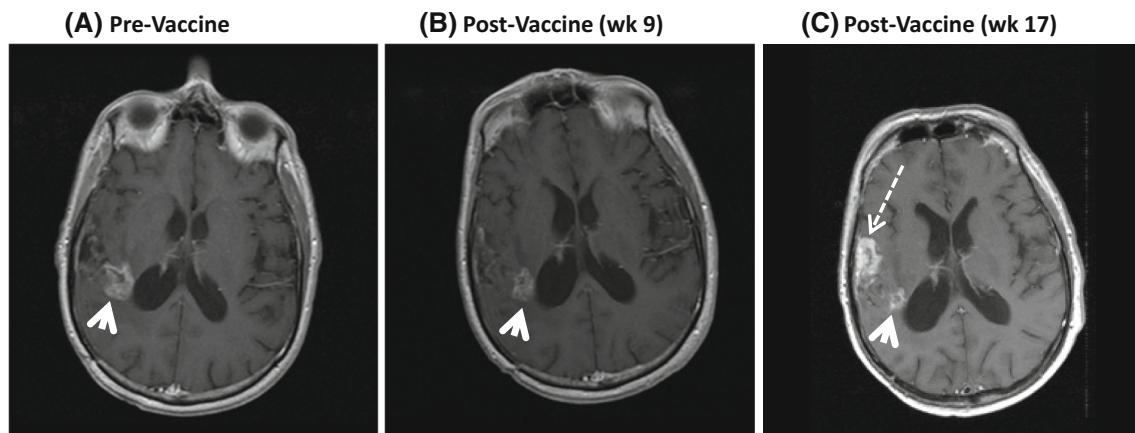
In addition, there is growing interest in evaluating immunotherapeutics within combinatorial regimens. There is a strong rationale for combining different immune checkpoint inhibitors with complementary mechanisms of immune activation as well as combining immune checkpoint inhibitors with active cancer vaccines. Although clinical trials evaluating such approaches are currently not active for neuro-oncology, several options are in advanced planning. Combination of immunotherapies with cytotoxic agents are also increasingly being considered based on the expected release of tumor-derived antigens following cell death induced by cytotoxic therapy, which can in turn be processed by immune cells and enhance their induction of anti-tumor immunity [24]. A striking example of such activity derives from the ability of cytotoxic radiotherapy to invoke an abscopal effect, characterized by tumor regression distant to the site of radiotherapy, when administered with ipilimumab [25].

### Complexity of radiographic worsening following immunotherapy

Given the recent marked increase in the application of immunotherapies for cancer indications, appreciation of the complexity to accurately assess response has grown in parallel. On the one hand, radiographic improvement is felt to provide a straightforward indication of anti-tumor effect because immunotherapies do not decrease tumor vessel permeability leading to pseudoresponse as been observed following anti-angiogenic agents [26]. On the other hand, worsened radiographic findings following administration of an immunotherapeutic may be more challenging to interpret. Although MRI worsening may reflect underlying tumor progression, at least for a subset of patients, early worsening of imaging findings may be followed by subsequent clinical benefit. For such patients, early

discontinuation of immunotherapy treatment due to worsened imaging findings assumed to be due to progressive underlying tumor may result in premature termination of a potentially active therapeutic option. There are two possible explanations for a lack of correlation between progressive imaging findings and ultimate therapeutic benefit. First, unlike radiation therapy or chemotherapy which are expected to exert a direct and rapid cytotoxic effect, immunotherapies exert an indirect anti-tumor effect via induction of an anti-tumor immune cell infiltrate which may take time to mobilize. Importantly, the kinetics of such anti-tumor immune responses may vary between different types of immunotherapies. Nonetheless, in this situation, some patients may have bona fide tumor progression early in the course of their therapy prior to subsequently responding to an immunotherapeutic. Second, a subset of patients may have pseudoprogressive radiographic findings following administration of an immunotherapeutic agent (Fig. 1). Potent anti-tumor immune responses inherently elicit inflammatory changes in the tumor microenvironment, including the macroscopic as well as infiltrative microscopic tumor regions, which may result in increased tumor vessel permeability leading in turn to increased contrast uptake as well as associated edema. Precedent for pseudoprogressive radiographic changes has been established for neuro-oncology based on experience following administration of temozolomide chemoradiotherapy for newly diagnosed glioblastoma patients. In this setting, pseudoprogression typically peak within 3 months and occurs in 20–30 % of patients [27, 28]. Appreciation of temozolomide chemoradiation associated pseudoprogression was a key factor underlying the widespread adoption of the radiologic assessment in neuro-oncology (RANO) criteria [29].

A growing number of clinical trials evaluating a wide array of immunotherapeutics across a spectrum of cancer indications demonstrate that a subset of patients treated with immunocytokines, cancer vaccines, T cell therapies and immune checkpoint inhibitors will achieve a radiographic response, durable stable disease or enhanced survival despite worsening of early imaging findings [21–23, 30–38]. The most extensive experience derives from recent clinical trials investigating CTLA-4 and PD-1/PD-L1 immune checkpoint inhibitors which are currently being widely evaluated for multiple cancer indications. Assessment of percent change in target lesion size over time for individual patients as plotted by spider plots reveals that a subset of patients may experience worsened radiographic findings, including the demonstration of new lesions, prior to achieving stable disease or radiographic response [21, 22, 35]. Furthermore, additional studies reveal that overall survival is not decreased among patients receiving immune checkpoint agents who exhibit worsening of early imaging



**Fig. 1** T1-weighted axial images following gadolinium administration in a patient with glioblastoma demonstrating pseudoprogressive changes after vaccination with autologous dendritic cells pulsed with glioma associated antigens and administered with poly-ICLC. **a** New nodular focus of enhancement in the medial right parietal lobe (*white arrowhead*) consistent with tumor progression prior to administration of vaccination. Note that the original tumor site which is located in the lateral right parietal lobe demonstrates minimal enhancement.

**b** 9 weeks after initiation of vaccination, the site of tumor progression is improved and the original tumor site is stable. **c** 17 weeks after vaccine initiation, the area of tumor progression demonstrates further improvement but the original site of tumor demonstrates significantly increased enhancement (*dashed white arrow*). Resection of the enhancing original tumor site revealed no evidence of mitotically active tumor but a marked infiltrate of CD68+ macrophages and CD8+ T cells [38]

findings. For example, 22 out of 227 (9.7 %) advanced melanoma patients treated with ipilimumab demonstrated early imaging findings that met WHO criteria for progressive disease yet later achieved either tumor stabilization ( $n = 17$ ) or partial response ( $n = 5$ ). Importantly, overall survival of these 22 patients was no different from that of patients who did not have early worsening of imaging findings [30]. Similarly 8 patients treated on a recently reported clinical trial of tremelimumab, an IgG2 CTLA-4 blocking antibody, ultimately achieved a partial response by response criteria in solid tumors (RECIST) despite meeting criteria for progression after the first cycle of therapy. Of note, median survival of these 8 patients (20 months) compared favorably to that of the full study population (10 months) [39].

Several clinical trials evaluating CTLA-4, PD-1 and PD-L1 inhibitory antibodies that have recently initiated will contribute to elucidating the frequency and impact of worsened early imaging findings among neuro-oncology patients treated with inhibitory immune checkpoint therapeutics. In a striking example reported over 10 years ago, a patient with widely metastatic melanoma including CNS lesions who was treated with MDX-CLTA-4, an IgG1 anti-CTLA-4 antibody, had significantly worsened enhancement on brain MRI soon after treatment. Extensive necrosis along with a small rim of viable tumor was noted at subsequent autopsy at many of the metastatic sites including the brain lesion [40]. Along the same lines, anecdotal reports highlight the occurrence of pseudoprogression among brain tumor patients treated with a variety of vaccine regimens [38, 41–43].

### Immune-related response criteria (irRC)

In recognition of the complexities associated with radiographic response assessment for patients undergoing treatment with immunotherapeutics, the immuno-oncology community recently drafted response assessment guidance referred to as the immune-related response criteria (irRC) [30, 44, 45]. In particular with regard to early progressive changes and their potential impact on premature discontinuation of therapy, the irRC incorporate the following important considerations: (1) a longer duration of time may be required for immunotherapies to exert measurable clinical activity at the tumor site compared to cytotoxic therapies; (2) immunotherapies may elicit radiographic responses after conventional progressive disease criteria have been met; (3) confirmation of progressive disease may be appropriate prior to discontinuation of immune therapy in some cases; (4) “clinically insignificant” progressive disease such as the development of small new lesions in the presence of other responsive lesions should be allowed; and, (5) clinical benefit should include durable stable disease. Furthermore, the irRC recommend continuation of immunotherapy pending confirmation of radiographic progression for clinically stable patients unless contraindicated medically [30].

In order to avoid premature termination of immune-based therapies prior to their ability to exert a potential therapeutic benefit, the irRC incorporate the novel concept of confirmation of progressive disease prior to therapy discontinuation for patients who are clinically stable. Of note such early progressive radiographic changes may



include either significant enlargement of existing lesions or the development of new lesions. In either case, irRC recommend that in medically stable patients, progression only be defined once follow-up imaging confirms radiographic findings that meet criteria for tumor progression. In such cases where radiographic progression is confirmed on follow-up imaging, the assigned actual date of progression should be back-dated to the date that the initial criteria for radiographic progression were met. Although the converse, confirmation of radiographic response is an accepted standard for most response assessment metrics in order to ensure that continuation of a given therapeutic is justified, confirmation of radiographic progression represents a novel paradigm shift in oncology. The down side of this approach is that therapy discontinuation and initiation of an alternative intervention will be delayed for those patients with early progressive radiographic changes who will not ultimately benefit from the administered immunotherapy. Nonetheless, continuation of currently prescribed immunotherapy pending confirmation of progression for clinically stable patients offers the potential advantage of more accurately interpreting possibly misleading early imaging changes and appears reasonable based on accumulated data suggesting that ultimate clinical benefit may be achieved at least in a subset of such patients. For much of neuro-oncology, including patients with either brain metastases or glioblastoma, durably effective therapeutic interventions are significantly limited; therefore adopting a paradigm of confirmation of radiographic progression among medically stable patients may be justified as a strategy to decrease the possibility of premature discontinuation of a promising therapeutic intervention.

### **Immunotherapy response assessment in neuro-oncology (iRANO) criteria**

Although the principles underlying the irRC provide important response assessment guidance for ongoing immunotherapy efforts in general medical oncology, modification of these criteria appear warranted in order to optimally and safely apply such guidance for neuro-oncology patients. Similarly, although the RANO criteria were drafted to provide more effective assessment of response for neuro-oncology patients undergoing therapy in the modern era, RANO alone may not fully address relevant considerations for neuro-oncology patients undergoing immunotherapy treatment. Thus, a multi-disciplinary and multinational group of neuro-oncology experts is currently drafting guidance for response assessment of neuro-oncology patients undergoing immune-based therapies. The immunotherapy response assessment in neuro-oncology (iRANO) criteria will integrate key components of

both irRC and RANO in order to take into account important nuances associated with neuro-oncology patients. A comparison of RANO, irRC and iRANO is summarized in Fig. 2. Like irRC, iRANO criteria will also advocate for confirmation of radiographic progression among medically stable patients. However, careful consideration is being included to specify temporal parameters and degree of allowed change in order to ensure patient safety given potential risks associated with robust inflammatory changes within the confines of the intracranial space. In addition, iRANO will include guidance for response assessment among patients with either enhancing or non-enhancing tumors. Furthermore and again in the context of preserving overall patient safety, iRANO will provide guidance on when to consider interrupting administration of an immunotherapeutic for patients with early radiographic progressive changes. Additional important considerations regarding corticosteroid dosing, the role of advanced MR and PET imaging techniques, the inclusion of metrics of neurologic function and overall quality of life, as well as guidance on immunocorrelative parameters to be prioritized in clinical research, will be addressed in the iRANO manuscript. Initial studies evaluating diffusion and perfusion MRI imaging following immunotherapy for neuro-oncology patients [46, 47], as well as PET imaging approaches [48, 49], suggest that these modalities may be of benefit in distinguishing tumor recurrence from pseudoprogression. Growing literature also supports the role of MR spectroscopy to predict inflammatory changes from true tumor progression [50, 51]. Monitoring serial assessments over time using advanced imaging techniques may also prove to be particularly helpful rather than single time point assessments [52]. Corticosteroid dosing is a particularly relevant issue for neuro-oncology patients being treated with immunotherapy agents. Corticosteroids are commonly prescribed to abrogate symptoms related to cerebral edema as well as autoimmune adverse events associated with some immune checkpoint inhibitors. Corticosteroids can further complicate response assessment because these agents are well known to impact imaging findings including reducing contrast uptake and edema. For this reason, RANO specifies that a CR requires patients to be on stable or decreased corticosteroid doses that are equivalent to no more than physiologic replacement, a PR requires stable or lowered corticosteroid dosing compared to baseline and progression can only be defined when patients are on stable or increased doses of corticosteroids [29]. Similar considerations will likely be required for iRANO. Finally, it is important to acknowledge that forthcoming iRANO criteria are intended as “best clinical management” guidance due to lack of sufficient clinical data and that these criteria are fully intended to be an initial set of recommendations with full expectation that the

## Key Considerations: RANO, irRC and iRANO

	RANO	irRC	iRANO
CR	<b>All</b> of the following required: no contrast enhancement; no corticosteroids; stable or improved T2 and clinical status; sustained for $\geq 4$ weeks	Complete disappearance of all lesions sustained for $\geq 4$ weeks	As per RANO
PR	<b>All</b> of the following required: $\geq 50\%$ reduction of bidimensional contrast lesions; stable or improved T2 changes, corticosteroid dosing and clinical status	Decrease in tumor burden* $\geq 50\%$ relative to baseline sustained for $\geq 4$ weeks	As per RANO
SD	<b>All</b> of the following required: $< 50\%$ decrease or $< 25\%$ increase bidimensional contrast lesions; stable or improved T2 changes, corticosteroid dosing and clinical status	Not meeting criteria for irCR or irPR, in absence of irPD compared with nadir	As per RANO
PD	<b>Any</b> of the followings: $\geq 25\%$ increase bidimensional contrast lesions; significant worsened T2 changes; new lesion; significant clinical decline	$\geq 25\%$ increase of tumor burden* compared with nadir (at any single time point) confirmed on follow-up imaging $\geq 4$ weeks later	As per RANO plus 1. Confirmation of progressive disease based on follow-up imaging for patients without significant clinical decline.

\*Tumor burden = sum of the products of perpendicular diameters for index lesions + sum of the perpendicular diameters of new measurable lesions

**Fig. 2** A summary comparison of RANO [29], irRC [30] and iRANO criteria

proposed criteria will be amended in the future to further enhance their utility as more significant experience with different types of immunotherapies is achieved for neuro-oncology patients and data from ongoing clinical trials is assessed.

Some of the critical questions that will require careful investigation as immunotherapeutics are further evaluated clinically for neuro-oncology patients include: (1) what are the frequency, clinical impact and kinetics of pseudoprogression associated with different forms of immunotherapy?; (2) how can advanced imaging approaches including diffusion and perfusion MRI, MRS and PET imaging better help evaluate response associated with immunotherapeutics including the ability to distinguish pseudoprogression from true progression?; (3) what immunocorrelative biomarkers should be prioritized and systematically evaluated in an effort to better predict patients more or less likely to respond to various immunotherapeutic strategies?; (4) can judicious administration of corticosteroid dosing lessen the impact of cerebral edema without compromising the efficacy of immunotherapeutics?; (5) which additional endpoints regarding immunocorrelative assessments as well as measures of neurologic function and quality of life are most relevant and should be included in upcoming immunotherapy clinical trials?

## Conclusions

Immune-based therapies offer great hope for cancer patients based on their ability to treat existing tumors as well as generate tumor-specific memory immune responses capable of preventing future recurrence. Nonetheless, interpretation of early progressive radiographic findings has proven challenging in that at least a subset of such patients ultimately achieves meaningful anti-tumor benefit. The immuno-oncology community has recently drafted recommendations to guide treating clinicians when confronted with early radiographic worsening that includes continuation of immunotherapy pending confirmation of progression for clinically stable patients. The immunotherapy response assessment for neuro-oncology (iRANO) criteria are currently in development and will integrate key recommendations from RANO with those of irRC in order to help optimally evaluate the therapeutic potential of different immunotherapeutic approaches for neuro-oncology patients.

## References

1. Coley WB (1893) The treatment of malignant tumors by repeated inoculations of Erysipelas, with a report of ten original cases. *Am J Med Sci* 105:487–511

2. Rosenberg SA, Yang JC, Restifo NP (2004) Cancer immunotherapy: moving beyond current vaccines. *Nat Med* 10:909
3. Kantoff PW, Higano CS, Shore ND et al (2010) Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 363:411–422
4. Reardon DA, Wucherpennig KW, Freeman G et al (2013) An update on vaccine therapy and other immunotherapeutic approaches for glioblastoma. *Expert Rev Vaccines* 12:597–615
5. Wen PY, Reardon DA, Phuphanich S, et al (2014) A randomized, double-blind, placebo-controlled phase 2 trial of dendritic cell (DC) vaccination with ICT-107 in newly diagnosed glioblastoma (GBM) patients, 2014 American Society of Clinical Oncology Annual Meeting, ASCO, Chicago, IL
6. Babu R, Adamson DC (2012) Rindopepimut: an evidence-based review of its therapeutic potential in the treatment of EGFRvIII-positive glioblastoma. *Core Evid* 7:93–103
7. Reardon DA, Li G, Recht L, et al (2013) ReACT: a phase II study of rindopepimut vaccine (CDX-110) plus bevacizumab in relapsed glioblastoma (GBM), 4th Quadrennial Meeting of the World Federation of Neuro-Oncology/18th Annual Meeting of the Society for Neuro-Oncology. Oxford Press, San Francisco, CA
8. Bloch O, Crane CA, Fuks Y et al (2014) Heat-shock protein peptide complex-96 vaccination for recurrent glioblastoma: a phase II, single-arm trial. *Neuro-Oncology* 16:274–279
9. Maude SL, Frey N, Shaw PA et al (2014) Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 371:1507–1517
10. Grupp SA, Kalos M, Barrett D et al (2013) Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* 368:1509–1518
11. Davila ML, Riviere I, Wang X et al (2014) Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med* 6:224ra25
12. Brentjens RJ, Davila ML, Riviere I et al (2013) CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med* 5:177ra38
13. Kochenderfer JN, Dudley ME, Feldman SA et al (2012) B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. *Blood* 119:2709–2720
14. Gilham DE, Debets R, Pule M et al (2012) CAR-T cells and solid tumors: tuning T cells to challenge an inveterate foe. *Trends Mol Med* 18:377–384
15. Ott PA, Hodi FS, Robert C (2013) CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clin Cancer Res* 19:5300–5309
16. Sznol M, Chen L (2013) Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. *Clin Cancer Res* 19:1021–1034
17. Hodi FS, O'Day SJ, McDermott DF et al (2010) Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 363:711–723
18. Robert C, Thomas L, Bondarenko I et al (2011) Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 364:2517–2526
19. Prieto PA, Yang JC, Sherry RM et al (2012) CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. *Clin Cancer Res* 18:2039–2047
20. Robert C, Ribas A, Wolchok JD et al (2014) Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* 384:1109–1117
21. Topalian SL, Hodi FS, Brahmer JR et al (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 366:2443–2454
22. Hamid O, Robert C, Daud A et al (2013) Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 369:134–144
23. Wolchok JD, Kluger H, Callahan MK et al (2013) Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 369:122–133
24. Shurin MR (2013) Dual role of immunomodulation by anticancer chemotherapy. *Nat Med* 19:20–22
25. Postow MA, Callahan MK, Barker CA et al (2012) Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 366:925–931
26. Chinot OL, Macdonald DR, Abrey LE et al (2013) Response assessment criteria for glioblastoma: practical adaptation and implementation in clinical trials of antiangiogenic therapy. *Curr Neurol Neurosci Rep* 13:347
27. Brandsma D, Stalpers L, Taal W et al (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol* 9:453–461
28. Radbruch A, Fladt J, Kickingereder P et al (2015) Pseudoprogression in patients with glioblastoma: clinical relevance despite low incidence. *Neuro-Oncol* 17(1):151–159
29. Wen PY, Macdonald DR, Reardon DA et al (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 28:1963–1972
30. Wolchok JD, Hoos A, O'Day S et al (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 15:7412–7420
31. Little RF, Pluda JM, Wyvill KM et al (2006) Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. *Blood* 107:4650–4657
32. van Baren N, Bonnet MC, Dreno B et al (2005) Tumoral and immunologic response after vaccination of melanoma patients with an ALVAC virus encoding MAGE antigens recognized by T cells. *J Clin Oncol* 23:9008–9021
33. Kruit WH, van Ojik HH, Brichard VG et al (2005) Phase 1/2 study of subcutaneous and intradermal immunization with a recombinant MAGE-3 protein in patients with detectable metastatic melanoma. *Int J Cancer* 117:596–604
34. Di Giacomo AM, Danielli R, Guidoboni M et al (2009) Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer Immunol Immunother* 58:1297–1306
35. Brahmer JR, Tykodi SS, Chow LQ et al (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 366:2455–2465
36. Topalian SL, Sznol M, McDermott DF et al (2014) Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol* 32:1020–1030
37. Hodi FS, Lawrence D, Lezcano C et al (2014) Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res* 2:632–642
38. Okada H, Kalinski P, Ueda R et al (2011) Induction of CD8+ T-cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with  $\alpha$ -type 1 polarized dendritic cells and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in patients with recurrent malignant glioma. *J Clin Oncol* 29:330–336
39. Kirkwood JM, Lorigan P, Hersey P et al (2010) Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. *Clin Cancer Res* 16:1042–1048
40. Hodi FS, Mihm MC, Soiffer RJ et al (2003) Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proc Natl Acad Sci USA* 100:4712–4717

41. Pollack IF, Jakacki RI, Butterfield LH et al (2014) Antigen-specific immune responses and clinical outcome after vaccination with glioma-associated antigen peptides and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in children with newly diagnosed malignant brainstem and non-brainstem gliomas. *J Clin Oncol* 32:2050–2058
42. Sampson JH, Heimberger AB, Archer GE et al (2010) Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. *J Clin Oncol* 28:4722–4729
43. Chiocca EA, Aguilar LK, Bell SD et al (2011) Phase IB study of gene-mediated cytotoxic immunotherapy adjuvant to up-front surgery and intensive timing radiation for malignant glioma. *J Clin Oncol* 29:3611–3619
44. Hoos A, Eggermont AM, Janetzki S et al (2010) Improved endpoints for cancer immunotherapy trials. *J Natl Cancer Inst* 102:1388–1397
45. Hoos A, Parmiani G, Hege K et al (2007) A clinical development paradigm for cancer vaccines and related biologics. *J Immunother* 30:1–15
46. Vrabec M, Van Cauter S, Himmelreich U et al (2011) MR perfusion and diffusion imaging in the follow-up of recurrent glioblastoma treated with dendritic cell immunotherapy: a pilot study. *Neuroradiology* 53:721–731
47. Stenberg L, Englund E, Wirestam R et al (2006) Dynamic susceptibility contrast-enhanced perfusion magnetic resonance (MR) imaging combined with contrast-enhanced MR imaging in the follow-up of immunogene-treated glioblastoma multiforme. *Acta Radiol* 47:852–861
48. Chiba Y, Kinoshita M, Okita Y et al (2012) Use of (11)C-methionine PET parametric response map for monitoring WT1 immunotherapy response in recurrent malignant glioma. *J Neurosurg* 116:835–842
49. Popperl G, Kreth FW, Herms J et al (2006) Analysis of 18F-FET PET for grading of recurrent gliomas: is evaluation of uptake kinetics superior to standard methods? *J Nucl Med* 47:393–403
50. Srinivasan R, Phillips JJ, Vandenberg SR et al (2010) Ex vivo MR spectroscopic measure differentiates tumor from treatment effects in GBM. *Neuro-Oncology* 12:1152–1161
51. Smith EA, Carlos RC, Junck LR et al (2009) Developing a clinical decision model: MR spectroscopy to differentiate between recurrent tumor and radiation change in patients with new contrast-enhancing lesions. *AJR* 192:W45–W52
52. Boxerman JL, Ellingson BM, Jeyapalan S, et al (2014) Longitudinal DSC-MRI for distinguishing tumor recurrence from pseudoprogression in patients with a high-grade glioma. *Am J Clin Oncol*. doi:[10.1097/COC.0000000000000156](https://doi.org/10.1097/COC.0000000000000156)